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(54) Title: USE OF IMIDAZOLYL CYCLIC ACETAL DERIVATIVES IN THE MANUFACTURE OF A MEDICAMENT FOR THE TREATMENT OF DISEASES MEDIATED BY THE ALK5 RECEPTORS

(57) Abstract: The use of imidazolyl-cyclic acetals as inhibitors of the transforming growth factor, ("TGF")- β signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the type I or activinlike kinase (ALK)-5 receptor are disclosed.

USE OF IMIDAZOLYL CYCLIC ACETAL DERIVATIVES IN THE MANUFACTURE OF A MEDICAMENT
FOR THE TREATMENT OF DISEASES MEDIATED BY THE ALK5 RECEPTORS

This invention relates to the use of imidazolyl-cyclic acetals as inhibitors of the transforming growth factor, ("TGF")- β signaling pathway, in particular, the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ("ALK")-5 receptor.

TGF- β 1 is the prototypic member of a family of cytokines including the TGF- β s, activins, inhibins, bone morphogenetic proteins and Müllerian-inhibiting substance, that signal through a family of single transmembrane serine/threonine kinase receptors. These receptors can be divided in two classes, the type I or activin like kinase (ALK) receptors and type II receptors. The ALK receptors are distinguished from the type II receptors in that the ALK receptors (a) lack the serine/threonine rich intracellular tail, (b) possess serine/threonine kinase domains that are very homologous between type I receptors, and (c) share a common sequence motif called the GS domain, consisting of a region rich in glycine and serine residues. The GS domain is at the amino terminal end of the intracellular kinase domain and is critical for activation by the type II receptor. Several studies have shown that TGF- β signaling requires both the ALK and type II receptors. Specifically, the type II receptor phosphorylates the GS domain of the type I receptor for TGF- β , ALK5, in the presence of TGF- β . The ALK5, in turn, phosphorylates the cytoplasmic proteins smad2 and smad3 at two carboxy terminal serines. The phosphorylated smad proteins translocate into the nucleus and activate genes that contribute to the production of extracellular matrix. Therefore, preferred compounds of this invention are selective in that they inhibit the type I receptor and thus matrix production.

Activation of the TGF- β 1 axis and expansion of extracellular matrix are early and persistent contributors to the development and progression of chronic renal disease and vascular disease. Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. Further, TGF- β 1 plays a role in the formation of fibronectin and plasminogen activator inhibitor-1, components of sclerotic deposits, through the action of smad3 phosphorylation by the TGF- β 1 receptor ALK5. Zhang Y., *et al*, *Nature*, 1998; 394(6696), 909-13; Usui T., *et al*, *Invest. Ophthalmol. Vis. Sci.*, 1998; 39(11), 1981-9.

Progressive fibrosis in the kidney and cardiovascular system is a major cause of suffering and death and an important contributor to the cost of health care. TGF- β 1 has been implicated in many renal fibrotic disorders. Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. TGF- β 1 is elevated in acute and chronic glomerulonephritis Yoshioka K., *et al*, *Lab. Invest.*, 1993; 68(2), 154-63, diabetic nephropathy Yamamoto, T., *et al*, 1993, *PNAS* 90, 1814-1818., allograft rejection, HIV nephropathy and angiotensin-induced nephropathy Border W.A., *et al*, *N. Engl. J. Med.*, 1994; 331(19), 1286-92. In these diseases the levels of TGF- β 1 expression coincide with the production of extracellular matrix. Three lines of evidence suggest a causal relationship between TGF- β 1 and the production of matrix. First, normal glomeruli, mesangial cells and non-renal cells can be induced to produce extracellular-matrix protein and inhibit protease activity by exogenous TGF- β 1 in vitro. Second, neutralizing anti-bodies against TGF- β 1 can prevent the accumulation of extracellular matrix in nephritic rats. Third, TGF- β 1 transgenic mice or in vivo transfection of the TGF- β 1 gene into normal rat kidneys resulted in the rapid development of glomerulosclerosis. Kopp J.B., *et al*, *Lab. Invest.*, 1996; 74(6), 991-1003.

Thus, inhibition of TGF- β 1 activity is indicated as a therapeutic intervention in chronic renal disease.

TGF- β 1 and its receptors are increased in injured blood vessels and are indicated in neointima formation following balloon angioplasty Saltis J., *et al*, *Clin. Exp. Pharmacol. Physiol.*, 1996; 23(3), 193-200. In addition TGF- β 1 is a potent stimulator of smooth muscle cell ("SMC") migration in vitro and migration of SMC in the arterial wall is a contributing factor in the pathogenesis of atherosclerosis and restenosis. Moreover, in multivariate analysis of the endothelial cell products against total cholesterol, TGF- β receptor ALK5 correlated with total cholesterol ($P < 0.001$) Blann A.D., *et al*, *Atherosclerosis*, 1996; 120(1-2), 221-6. Furthermore, SMC derived from human atherosclerotic lesions have an increased ALK5/TGF- β type II receptor ratio. Because TGF- β 1 is over-expressed in fibroproliferative vascular lesions, receptor-variant cells would be allowed to grow in a slow, but uncontrolled fashion, while overproducing extracellular matrix components McCaffrey T.A., *et al*, Jr., *J. Clin. Invest.*, 1995; 96(6), 2667-75. TGF- β 1 was immunolocalized to non-foamy macrophages in atherosclerotic lesions where active matrix synthesis occurs, suggesting that non-foamy macrophages may participate in modulating matrix gene expression in atherosclerotic remodeling via a TGF- β -dependent mechanism. Therefore, inhibiting the action of TGF- β 1 on ALK5 is also indicated in atherosclerosis and restenosis.

TGF- β is also indicated in wound repair. Neutralizing antibodies to TGF- β 1 have been used in a number of models to illustrate that inhibition of TGF- β 1 signaling is beneficial in restoring function after injury by limiting excessive scar formation during the healing process. For example, neutralizing antibodies to TGF- β 1 and TGF- β 2 reduced scar formation and improved the cytoarchitecture of the neodermis by reducing the number of monocytes and macrophages as well as decreasing dermal fibronectin and collagen deposition in rats Shah M., *J. Cell. Sci.*, 1995, 108, 985-1002. Moreover, TGF- β antibodies also improve healing of corneal wounds in rabbits Moller-Pedersen T., *Curr. Eye Res.*, 1998, 17, 736-747, and accelerate wound healing of gastric ulcers in the rat, Ernst H., *Gut*, 1996, 39, 172-175. These data strongly suggest that limiting the activity of TGF- β would be beneficial in many tissues and suggest that any disease with chronic elevation of TGF- β would benefit by inhibiting smad2 and smad3 signaling pathways.

TGF- β is also implicated in peritoneal adhesions Saed G.M., *et al*, *Wound Repair Regeneration*, 1999 Nov-Dec, 7(6), 504-510. Therefore, inhibitors of ALK5 would be beneficial in preventing peritoneal and sub-dermal fibrotic adhesions following surgical procedures.

TGF β 1-antibodies prevent transplanted renal tumor growth in nude mice through what is thought to be an anti-angiogenic mechanism Ananth S., *et al*, *Journal Of The American Society Of Nephrology Abstracts*, 9: 433A(Abstract). While the tumor itself is not responsive to TGF- β , the surrounding tissue is responsive and supports tumor growth by neovascularization of the TGF- β secreting tumor. Thus, antagonism of the TGF- β pathway should prevent metastasis growth and reduce cancer burden.

WO 98/56788 discloses imidazolyl-cyclic acetals as inhibitors of tumor necrosis factor (TNF) and their use in e.g. the treatment of asthma and joint inflammation.

Surprisingly, it has now been discovered that the imidazolyl-cyclic acetals disclosed in WO 98/56788 function as potent and selective non-peptide inhibitors of ALK5 kinase and

therefore, have utility in the treatment and prevention of various disease states mediated by ALK5 kinase mechanisms, such as chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, and restenosis.

According to the invention there is provided a method of treatment of a disease mediated by the ALK5 receptor in mammals, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of an imidazolyl-cyclic acetal as disclosed in WO 98/56788.

The invention also provides the use of an imidazolyl-cyclic acetal as disclosed in WO98/56788 in therapy.

The invention further provides the use of an imidazolyl-cyclic acetal as disclosed in WO 98/56788, in the manufacture of a medicament for the treatment of a disease mediated by the ALK5 receptor in mammals.

The present invention includes the use of all those compounds generically disclosed by WO 98/56788 as well as those compounds that are specifically exemplified.

Particular group of compounds which may be mentioned for use in the method of the invention included those compounds wherein:

- i) the 5-position of the imidazolyl is substituted by 6-methylpyridin-2-yl; and/or
- ii) the 4-position of the imidazolyl is substituted by phenyl optionally substituted by halo, or phenyl fused with a 5- to 7-membered aromatic or non-aromatic ring wherein said ring contains up to three heteroatoms, independently selected from N, O and S, for example benzo[1,3]dioxolyl, 2,3-dihydrobenzo[1,4]dioxinyl, benzoxazolyl, benzothiazolyl, benzo[1,2,5]oxadiazolyl, benzo[1,2,5]thiadiazolyl or dihydrobenzofuranyl, or alternatively benzo[1,3]dioxolyl, 2,3-dihydrobenzo[1,4]dioxinyl, benzoxazolyl, benzothiazolyl, benzo[1,2,5]oxadiazolyl, benzo[1,2,5]thiadiazolyl, dihydrobenzofuranyl, quinoxaliny, benzimidazolyl, C₁₋₆ alkylbenzimidazolyl or [1,2,4]triazolo[1,5-a]pyridyl; and/or
- iii) the imidazolyl ring nitrogens are unsubstituted or may be optionally substituted by C₁₋₆ alkyl.

Those compounds of WO 98/56788 in which the 5-position of the imidazolyl is substituted by 6-methylpyridin-2-yl are novel *per se* and as such these compounds and their pharmaceutically acceptable salts, and pharmaceutical compositions comprising said compounds and a pharmaceutically acceptable carrier or diluent, form further aspects of the invention.

The compounds for use in the invention preferably have a molecular weight of less than 800.

Particular compounds for use according to the invention include those mentioned in the examples and their pharmaceutically acceptable salts.

Suitable pharmaceutically acceptable salts of the compounds for use in the invention include, but are not limited to, salts with inorganic acids such as hydrochloride, sulfate, phosphate, diphosphate, hydrobromide, and nitrate, or salts with an organic acid such as malate, maleate, fumarate, tartrate, succinate, citrate, acetate, lactate, methanesulfonate, p-toluenesulfonate, palmitate, salicylate and stearate.

Some of the compounds may be crystallised or recrystallised from solvents such as aqueous and organic solvents. In such cases solvates may be formed. This invention includes within its scope the use of stoichiometric solvates including hydrates as well as compounds containing variable amounts of water that may be produced by processes such as lyophilisation.

5 Certain of the compounds may exist in the form of optical isomers, e.g. diastereoisomers and mixtures of isomers in all ratios, e.g. racemic mixtures. The invention includes the use of all such forms, in particular the pure isomeric forms. The different isomeric forms may be separated or resolved one from the other by conventional methods, or any given isomer may be obtained by conventional synthetic methods or by stereospecific or asymmetric syntheses.

10 Since the compounds are intended for use in pharmaceutical compositions it will readily be understood that they are each preferably provided in substantially pure form, for example at least 60% pure, more suitably at least 75% pure and preferably at least 85%, especially at least 98% pure (% are on a weight for weight basis). Impure preparations of the compounds may be used for preparing the more pure forms used in the pharmaceutical compositions; these less pure
15 preparations of the compounds should contain at least 1%, more suitably at least 5% and preferably at least 10% of the compounds or pharmaceutically acceptable derivative thereof.

The term "C₁₋₆alkyl" as used herein whether on its own or as part of a larger group e.g. C₁₋₆alkoxy, means a straight or branched chain radical of 1 to 6 carbon atoms, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl and tert-butyl.
20

C₁₋₆haloalkyl groups may contain one or more halo atoms, a particular C₁₋₆haloalkyl group that may be mentioned in CF₃.

The terms "halo" or "halogen" are used interchangeably herein to mean radicals derived from the elements chlorine, fluorine, iodine and bromine.

25 The term "cycloalkyl" as used herein means cyclic radicals, preferably of 3 to 7 carbons, including but not limited to cyclopropyl, cyclopentyl and cyclohexyl.

The term "ALK5 inhibitor" as used herein means a compound, other than inhibitory smads, e.g. smad6 and smad7, which selectively inhibits the ALK5 receptor preferentially over p38 or type II receptors.

30 The term "ALK5 mediated disease state" as used herein means any disease state which is mediated (or modulated) by ALK5, for example a disease which is modulated by the inhibition of the phosphorylation of smad 2/3 in the TGF- β 1 signaling pathway.

The term "ulcers" as used herein includes but is not limited to, diabetic ulcers, chronic ulcers, gastric ulcers, and duodenal ulcers.

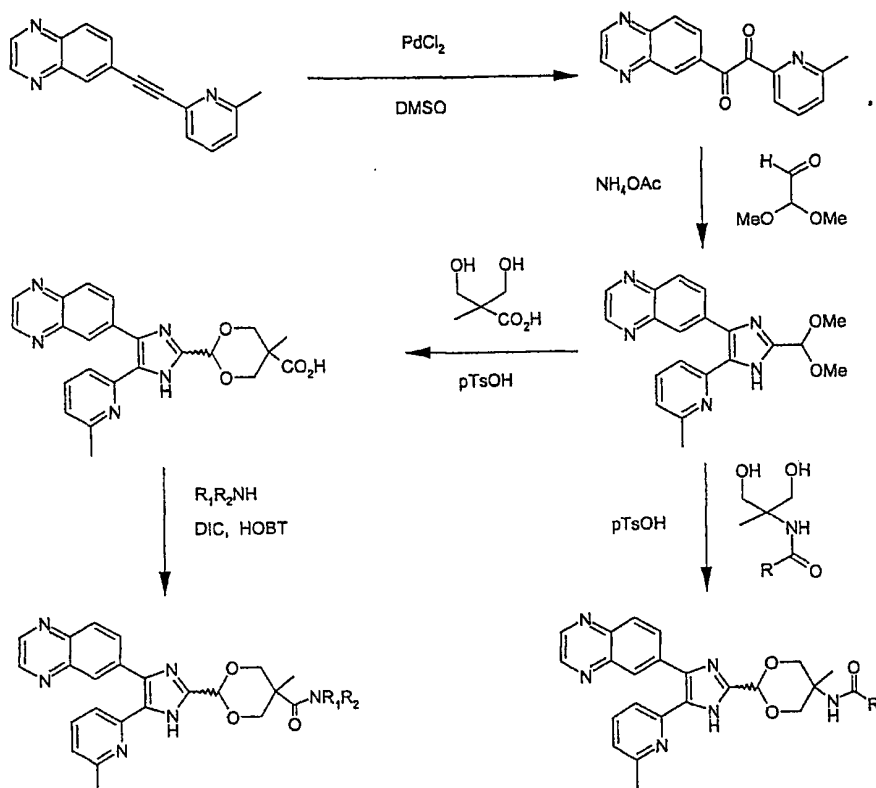
35 The compounds for use in the invention may be prepared by art-recognized procedures from known or commercially available starting materials as described in WO 98/56788. In particular the novel compounds of the invention may be prepared as illustrated in Scheme 1. The acetylene is oxidised to the diketone with PdCl₂ in DMSO. The diketone is then condensed with glyoxal-1,1-dimethylacetal and ammonium acetate to give the imidazolyl dimethylacetal.

40 Condensation with 2,2-bis(hydroxymethyl)propanoic acid in the presence of pTsOH gives the dioxane carboxylic acid, which can then be coupled with the appropriate amine, using DIC and HOBT, to give the dioxane carboxylic amide. Alternatively the imidazolyl dimethylacetal can be

condensed with the appropriate amidopropane diol, in the presence of pTsOH, to give the amidodioxane.

Scheme 1

5



Further details for the preparation of compounds of the invention are found in the examples.

During the synthesis of the compounds of the invention labile functional groups in the intermediate compounds, e.g. hydroxy, carboxy and amino groups, may be protected. A comprehensive discussion of the ways in which various labile functional groups may be protected and methods for cleaving the resulting protected derivatives is given in for example *Protective Groups in Organic Chemistry*, T.W. Greene and P.G.M. Wuts, (Wiley-Interscience, New York, 2nd edition, 1991).

The compounds of the invention may be prepared singly or as compound libraries comprising at least 2, for example 5 to 1,000 compounds, and more preferably 10 to 100 compounds of the invention. Libraries of compounds may be prepared by a combinatorial 'split and mix' approach or by multiple parallel synthesis using either solution phase or solid phase chemistry, by procedures known to those skilled in the art.

Thus according to a further aspect of the invention there is provided a compound library comprising at least 2 compounds of the invention or pharmaceutically acceptable salts thereof.

ALK5-mediated disease states which may be treated according to the invention include, but are not limited to, chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal abrasion, any disease wherein fibrosis is a major component, including, but not limited to lung fibrosis and liver fibrosis, and restenosis.

By the term "treating" is meant either prophylactic or therapeutic therapy.

According to a further aspect of the present invention there is provided a method of inhibiting the TGF- β signaling pathway in mammals, for example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor, which method comprises administering to a mammal in need of such treatment, an effective amount of an imidazolyl-cyclic acetal as disclosed in WO 98/56788.

According to a further aspect of the present invention there is provided a method of inhibiting matrix formation in mammals by inhibiting the TGF- β signalling pathway, for example, inhibiting the phosphorylation of smad2 or smad3 by the type I or activin-like kinase ALK5 receptor, which method comprises administering to a mammal in need of such treatment, an effective amount of an imidazolyl-cyclic acetal as disclosed in WO 98/56788.

The imidazolyl-cyclic acetals may be administered in conventional dosage forms prepared by combining with standard pharmaceutical carriers or diluents according to conventional procedures well known in the art. These procedures may involve mixing, granulating and compressing or dissolving the ingredients as appropriate to the desired preparation.

The pharmaceutical compositions of the invention may be formulated for administration by any route, and include those in a form adapted for oral, topical or parenteral administration to mammals including humans.

The compositions may be in the form of tablets, capsules, powders, granules, lozenges, creams or liquid preparations, such as oral or sterile parenteral solutions or suspensions.

The topical formulations of the present invention may be presented as, for instance, ointments, creams or lotions, eye ointments and eye or ear drops, impregnated dressings and aerosols, and may contain appropriate conventional additives such as preservatives, solvents to assist drug penetration and emollients in ointments and creams.

The formulations may also contain compatible conventional carriers, such as cream or ointment bases and ethanol or oleyl alcohol for lotions. Such carriers may be present as from about 1% up to about 98% of the formulation. More usually they will form up to about 80% of the formulation.

Tablets and capsules for oral administration may be in unit dose presentation form, and may contain conventional excipients such as binding agents, for example syrup, acacia, gelatin, sorbitol, tragacanth, or polyvinylpyrrolidone; fillers, for example lactose, sugar, maize-starch, calcium phosphate, sorbitol or glycine; tableting lubricants, for example magnesium stearate, talc, polyethylene glycol or silica; disintegrants, for example potato starch; or acceptable wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in normal pharmaceutical practice. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions, emulsions, syrups or elixirs, or may be

presented as a dry product for reconstitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives, such as suspending agents, for example sorbitol, methyl cellulose, glucose syrup, gelatin, hydroxyethyl cellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats, emulsifying agents, for example
5 lecithin, sorbitan monooleate, or acacia; non-aqueous vehicles (which may include edible oils), for example almond oil, oily esters such as glycerine, propylene glycol, or ethyl alcohol; preservatives, for example methyl or propyl *p*-hydroxybenzoate or sorbic acid, and, if desired, conventional flavouring or colouring agents.

Suppositories will contain conventional suppository bases, e.g. cocoa-butter or other
10 glyceride.

For parenteral administration, fluid unit dosage forms are prepared utilizing the compound and a sterile vehicle, water being preferred. The compound, depending on the vehicle and concentration used, can be either suspended or dissolved in the vehicle. In preparing
15 solutions the compound can be dissolved in water for injection and filter sterilised before filling into a suitable vial or ampoule and sealing.

Advantageously, agents such as a local anaesthetic, preservative and buffering agents can be dissolved in the vehicle. To enhance the stability, the composition can be frozen after filling into the vial and the water removed under vacuum. The dry lyophilized powder is then sealed in the vial and an accompanying vial of water for injection may be supplied to reconstitute the
20 liquid prior to use. Parenteral suspensions are prepared in substantially the same manner except that the compound is suspended in the vehicle instead of being dissolved and sterilization cannot be accomplished by filtration. The compound can be sterilised by exposure to ethylene oxide before suspending in the sterile vehicle. Advantageously, a surfactant or wetting agent is included in the composition to facilitate uniform distribution of the compound.

The compositions may contain from 0.1% by weight, preferably from 10-60% by weight,
25 of the active material, depending on the method of administration. Where the compositions comprise dosage units, each unit will preferably contain from 50-500 mg of the active ingredient. The dosage as employed for adult human treatment will preferably range from 100 to 3000 mg per day, for instance 1500 mg per day depending on the route and frequency of administration.
30 Such a dosage corresponds to 1.5 to 50 mg/kg per day. Suitably the dosage is from 5 to 20 mg/kg per day.

It will be recognized by one of skill in the art that the optimal quantity and spacing of individual dosages will be determined by the nature and extent of the condition being treated, the form, route and site of administration, and the particular mammal being treated, and that such
35 optimums can be determined by conventional techniques. It will also be appreciated by one of skill in the art that the optimal course of treatment, i.e., the number of doses given per day for a defined number of days, can be ascertained by those skilled in the art using conventional course of treatment determination tests.

No toxicological effects are indicated when an imidazolyl-cyclic acetal as disclosed in
40 WO 98/56788 is administered in the above-mentioned dosage range.

All publications, including, but not limited to, patents and patent applications cited in this specification, are herein incorporated by reference as if each individual publication were

specifically and individually indicated to be incorporated by reference herein as though fully set forth.

The following examples are to be construed as merely illustrative and not a limitation on the scope of the invention in any way.

5

Abbreviations

- TBuOMe – *tert*-butylmethoxide
 CuI – copper(I) iodide
 DMF - dimethylformamide
 10 DMSO - dimethylsulfoxide
 EtOAc – ethyl acetate
 EtOH – ethanol
 H₂O – water
 HOAc – acetic acid
 15 K₂CO₃ – potassium carbonate
 MeOH - methanol
 MgSO₄ – magnesium sulphate
 NaOH – sodium hydroxide
 NH₃ - ammonia
 20 NH₄OAc – ammonium acetate
 iPr₂NH – diisopropylamine
 PdCl₂ – palladium(II) chloride
 Pd(PPh₃)₂Cl₂ – dichlorobis(triphenylphosphine)palladium(0)
 Pd(PPh₃)₄ – tetrakis(triphenylphosphine)palladium(0)
 25 THF – tetrahydrofuran
 TMEDA – *N,N,N',N'*- tetramethylethylenediamine
 pTsOH – *para*-toluenesulfonic acid

Description 1: 4-Bromo-1,2-diaminobenzene (D1)

- 30 A stirred suspension of 4-bromo-2-nitroaniline (28.3 g, 130 mmole) in a mixture of EtOH (275 ml) and H₂O (320 ml) was heated at 90°C until all material had dissolved, then treated with sodium dithionite (136 g, 780 mmole). The mixture instantly decolourised and was allowed to cool. The EtOH was removed *in vacuo* and the residue extracted with dichloromethane (3x). The organics were combined, dried (MgSO₄) and concentrated to dryness *in vacuo* giving the
 35 title compound as a beige solid (17.0 g, 70%); MS: m/z (MH) = 187, 189.

Description 2: 6-Bromoquinoxaline (D2)

- A stirred suspension of D1 (33.3 g, 178 mmole) and glyoxal sodium bisulfite addition compound (71.1 g, 267 mmole) in H₂O was heated at 65°C under argon for 4 h. On cooling the mixture was
 40 adjusted to pH14 with 2M NaOH solution and extracted with EtOAc (2x). The organics were combined, dried (MgSO₄) and concentrated to dryness *in vacuo*. Purification by flash silica chromatography, eluting with EtOAc / 60-80°C petrol gradient, gave the title compound as a pale orange solid (32.9 g, 88%); MS: m/z (MH) = 209, 211.

Description 3: 6-Trimethylsilyl ethynylquinoxaline (D3)

A stirred solution of D2 (12.4 g, 59.3 mmole) in anhydrous THF (120 ml) was bubbled with argon for 20 min, then treated with CuI (1.13 g, 5.93 mmole) and Pd(PPh₃)₂Cl₂ (0.83 g, 1.19 mmole) and stirring continued under argon. Trimethylsilylacetylene was added (31.8 ml, 225 mmole) followed by dropwise addition of ⁱPr₂NH (51.0 ml, 380 mmole) and stirring continued. After 18 h the mixture was partitioned between EtOAc and H₂O. The organic phase was separated, washed with H₂O and brine, dried (MgSO₄) and concentrated to dryness *in vacuo*. Purification by flash silica chromatography, eluting with 20% EtOAc / 40-60°C petrol, gave the title compound as a dark orange solid (11.7 g, 87%); MS: m/z (MH) = 227.

Description 4: 6-Ethynylquinoxaline (D4)

A solution of D3 (11.7 g, 51.8 mmole) in MeOH (275 ml) was treated with K₂CO₃ (21.4 g, 155 mmole) and stirred at room temperature under argon for 1 h. The mixture was then filtered and concentrated to dryness *in vacuo*. The residue was partitioned between EtOAc and H₂O, the organic layer separated, washed with brine, dried (MgSO₄) and concentrated to dryness *in vacuo* giving the title compound as a beige solid (7.19 g, 91%); MS: m/z (MH) = 155.

Description 5: 6-(6-Methylpyridin-2-yl ethynyl) quinoxaline (D5)

A stirred solution of D4 (6.0 g, 39.0 mmole) in a mixture of THF (135 ml) and TMEDA (135 ml) was treated with 2-bromo-6-methylpyridine (8.86 ml, 77.9 mmole) and bubbled with argon for 10 min. CuI (0.74 g, 3.90 mmole) and Pd(PPh₃)₄ (2.25 g, 1.95 mmole) were added and the mixture heated at 55°C under argon for 7 h. On cooling, a saturated aqueous solution of NH₄Cl was added and the mixture extracted with EtOAc. The organic phase was separated, washed with H₂O and brine, dried (MgSO₄) then concentrated to dryness *in vacuo*. The crude material was purified by flash silica chromatography, eluting with EtOAc / 60-80°C petrol gradient, giving the title compound as a yellow solid (7.65 g, 80%); MS: m/z (MH) = 246.

Description 6: 1-(6-Methylpyridin-2-yl)-2-quinoxalin-6-yl ethane-1,2-dione (D6)

A stirred solution of D5 (7.65 g, 31.2 mmole) in DMSO (90 ml) was treated with PdCl₂ (0.55 g, 3.1 mmole) and heated at 140°C for 4 h, then cooled to room temperature and partitioned between H₂O and EtOAc. The organic phase was separated and the aqueous extracted with further EtOAc (2x). The combined organics were washed with H₂O and brine, then dried (MgSO₄) and concentrated to dryness *in vacuo*. The crude material was purified by flash silica chromatography, eluting with 50% EtOAc / 40-60°C petrol, to afford the title compound as a yellow solid (4.32 g, 50%); MS: m/z (MH) = 278.

Description 7: 6-[2-(1,1-Dimethoxymethyl)-5-(6-methylpyridin-2-yl)-3H-imidazol-4-yl]quinoxaline (D7)

A stirred suspension of D6 (4.86 g, 17.5 mmole) in ^tBuOMe (24 ml) was treated with a solution of glyoxal-1,1-dimethylacetal (9.0 ml, 35.1 mmole, 45% solution in ^tBuOMe), followed by a solution of NH₄OAc (6.75 g, 87.7 mmole) in MeOH (13 ml). The resulting solution was stirred at room temperature under argon for 17 h, then partitioned between H₂O and EtOAc. The

organic phase was separated and the aqueous extracted with further EtOAc (2x). The combined organics were dried (MgSO_4) then concentrated to dryness *in vacuo* to give the title compound as an orange gum (6.30 g, 99%); MS: m/z (MH) = 362.

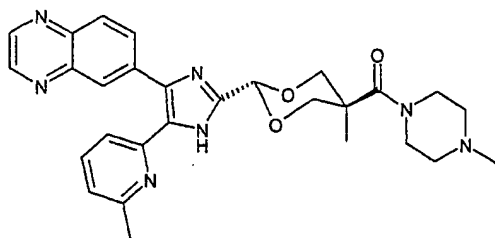
5 **Description 8: 5-Methyl-2-[5-(6-methylpyridin-2-yl)-4-quinoxalin-6-yl-1*H*-imidazol-2-yl]-[1,3]-dioxane-5-carboxylic acid (D8)**

A stirred solution of D7 (0.50 g, 1.39 mmole) in anhydrous THF (20 ml) was treated with 2,2-bis(hydroxymethyl) propionic acid (2.0 g, 14.9 mmole) and pTsOH (250 mg, 1.45 mmole) and heated at reflux under argon for 5 days. The mixture was then cooled and loaded onto SCX
10 resin. The resin was washed with dichloromethane (20 ml), 50% MeOH / dichloromethane (20 ml) and MeOH (20 ml), then the product was eluted with a solution of 1% NH_3 / MeOH. Concentration to dryness *in vacuo* afforded the title compound as an orange solid (0.51 g, 85%); MS: m/z (MH) = 432.

15 **Description 9: 2-Benzamido-2-methyl-1,3-propanediol (D9)**

A stirred solution of benzoic acid (1.0 g, 8.20 mmole) in anhydrous DMF (25 ml) was treated with EDC (2.35 g, 12.3 mmole) and HOAT (1.67 g, 12.3 mmole) and stirred under argon at room temperature for 20 min. 2-Amino-2-methyl-1,3-propanediol (1.72 g, 16.4 mmole) was added and stirring continued for 42 h. The mixture was then loaded onto SCX resin and the crude product
20 eluted with 50% MeOH / dichloromethane. Purification by flash silica chromatography, eluting with MeOH / dichloromethane gradient, gave the title compound as a white solid (1.29 g, 75%); MS: m/z (MH) = 208.

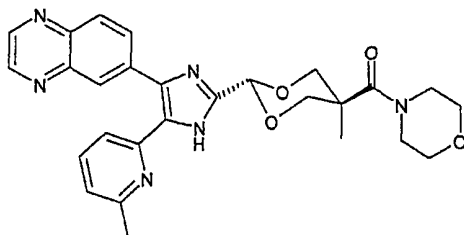
25 **Example 1: *Trans* 5-methyl-2-[5-(6-methylpyridin-2-yl)-4-quinoxalin-6-yl-1*H*-imidazol-2-yl]-[1,3]-dioxane-5-carboxylic acid (4-methylpiperazin-1-yl) amide (E1)**



A solution of D8 (100 mg, 0.23 mmole) in anhydrous DMF (5 ml) was treated with DIC (44 mg, 0.35 mmole) and HOBT. H_2O (53 mg, 0.35 mmole) and stirred at room temperature under argon.
30 After 30 min a solution of N-methylpiperazine (46 mg, 0.46 mmole) in anhydrous DMF (1 ml) was added and stirring continued for 48 h. Methylisocyanate scavenger resin and dichloromethane (10 ml) were added and stirring continued. After 24 h, the mixture was filtered and concentrated to dryness *in vacuo*. The crude product was passed through SAX resin eluting
35 with dichloromethane. Concentration to dryness *in vacuo* gave the title compound as a yellow solid (14 mg, 12%); MS: m/z (MH) = 514. ^1H NMR (400 MHz, CDCl_3): δ ppm: 8.81 (m, 2H), 8.40 (s, 1H), 8.13-8.08 (m, 2H), 7.41-7.27 (m, 2H), 7.00 (d, 1H), 5.78 (s, 1H), 4.80 (d, 2H), 3.73-

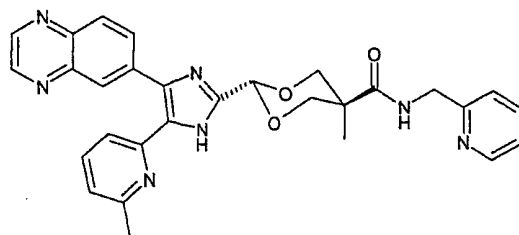
3.62 (m, 6H), 2.59 (s, 3H), 2.44 (br. s, 4H), 2.31 (s, 3H), 1.15 (s, 3H). imidazole NH not discernible.

Example 2: *Trans* 5-methyl-2-[5-(6-methylpyridin-2-yl)-4-quinoxalin-6-yl-1*H*-imidazol-2-yl]-[1,3]-dioxane-5-carboxylic acid morpholine amide (E2)



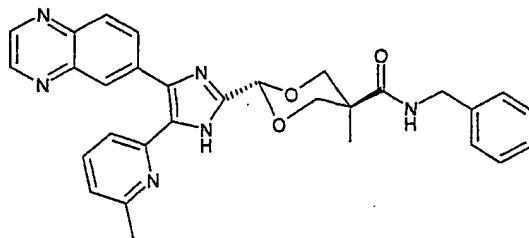
The title compound was prepared from D8 (100 mg, 0.23 mmole) and morpholine (40 mg, 0.46 mmole) using a similar procedure to E1, as a yellow solid (46 mg, 40%); MS: m/z (MH) = 501. ^1H NMR (400 MHz, CDCl_3): δ ppm): 8.83 (m, 2H), 8.39 (s, 1H), 8.15-8.07 (m, 2H), 7.41 (dd, 1H), 7.32 (br. d, 1H), 7.01 (d, 1H), 5.79 (s, 1H), 4.79 (d, 2H), 4.23 (s, 1H), 3.74-3.67 (m, 10H), 2.57 (s, 3H), 1.16 (s, 3H).

Example 3: *Trans* 5-methyl-2-[5-(6-methylpyridin-2-yl)-4-quinoxalin-6-yl-1*H*-imidazol-2-yl]-[1,3]-dioxane-5-carboxylic acid (pyridin-2-ylmethyl) amide (E3)



The title compound was prepared from D8 (130 mg, 0.30 mmole) and 2-aminomethylpyridine (64 mg, 0.60 mmole) using a similar procedure to E1. The crude material was purified using the Paralex Flex, rather than using SAX resin, giving the trifluoroacetate salt of the title compound as a yellow / brown solid (5 mg, 3%); MS: m/z (MH) = 522. ^1H NMR (400 MHz, CDCl_3 , trifluoroacetate salt): δ ppm): 8.92 (s, 1H), 8.88 (s, 1H), 8.76 (m, 1H), 8.65 (d, 1H), 8.32 (dd, 1H), 8.27 (s, 1H), 8.18 (d, 1H), 8.00-7.90 (m, 3H), 7.74 (dd, 1H), 7.48 (d, 1H), 7.41 (d, 1H), 5.91 (s, 1H), 4.89 (d, 2H), 4.38 (d, 2H), 3.85 (d, 2H), 2.79 (s, 3H), 1.00 (s, 3H). imidazole NH not discernible.

Example 4: *Trans* 5-methyl-2-[5-(6-methylpyridin-2-yl)-4-quinoxalin-6-yl-1*H*-imidazol-2-yl]-[1,3]-dioxane-5-carboxylic acid benzyl amide (E4)

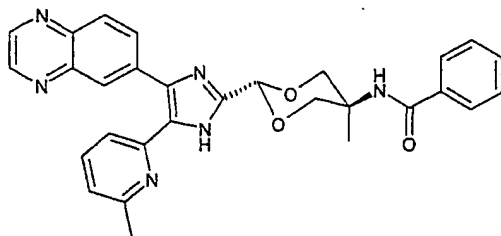


5

The trifluoroacetate salt of the title compound was prepared from D8 (250 mg, 0.58 mmole) and benzylamine (124 mg, 1.16 mmole) using a similar procedure to E3, as a yellow / brown solid (28 mg, 8%); MS: m/z (MH) = 521. ^1H NMR (400 MHz, CDCl_3 , trifluoroacetate salt): δ ppm): 8.97 (s, 1H), 8.91 (s, 1H), 8.27-8.24 (m, 2H), 8.01 (d, 1H), 7.92 (dd, 1H), 7.50 (d, 1H), 7.43 (d, 1H), 7.26-7.24 (m, 2H), 7.06 (dd, 2H), 6.89 (dd, 1H), 5.91 (s, 1H), 4.58 (d, 2H), 4.50 (d, 2H), 3.86 (d, 2H), 2.81 (s, 3H), 1.09 (s, 3H). amide and imidazole NHs not discernible.

Example 5: *Trans* 5-methyl-2-[5-(6-methylpyridin-2-yl)-4-quinoxalin-6-yl-1*H*-imidazol-2-yl]-[1,3]-dioxane-5-benzamide (E5)

15



The title compound was prepared from D7 (100 mg, 0.28 mmole) and D9 (116 mg, 0.55 mmole) using a similar procedure to D8. The crude material was purified using the Paralex Flex, giving the trifluoroacetate salt of the title compound as a yellow / brown solid (12 mg, 9%); MS: m/z (MH) = 507. ^1H NMR (400 MHz, CDCl_3 , trifluoroacetate salt): δ ppm): 8.92 (d, 1H), 8.87 (d, 1H), 8.24 (d, 1H), 8.19 (d, 1H), 7.98 (dd, 1H), 7.89-7.85 (m, 3H), 7.47-7.34 (m, 5H), 5.86 (s, 1H), 4.61 (d, 2H), 3.79 (d, 2H), 2.83 (s, 3H), 1.44 (s, 3H). amide and imidazole NHs not discernible.

25

Biological Data

The biological activity of the compounds may be assessed using the following assays:

Method for evaluating ALK5 kinase phosphorylation of smad3

Basic Flash-Plates (NEN Life Sciences) were coated by pipetting 100 micro liter of 0.1 molar sodium bicarbonate (pH 7.6), containing 150 nanograms of the fusion protein glutathion-S-transferase-smad3/100 micro liter of coating buffer. Plates were covered and incubated at room

30

temperature for 10-24 hours. Then the plates were washed 2 times with 200 micro liter of coating buffer (0.1 molar sodium bicarbonate) and allowed to air dry for 2-4 hours.

For the phosphorylation reaction each well received 100 microliter containing 50 millimolar HEPES buffer (pH 7.4); 5 millimolar $MgCl_2$; 1 millimolar $CaCl_2$; 1 millimolar dithiothreitol; 100 micromolar guanosine triphosphate; 0.5 micro Ci/well gamma³³P-adenosine triphosphate (NEN Life Sciences) and 400 nanograms of a fusion protein of glutathion -S-transferase at the N-terminal end of the kinase domain of ALK5 (GST-ALK5). Background counts were measured by not adding any GST-ALK5. Inhibitors of ALK5 were evaluated by determining the activity of the enzyme in the presence of various compounds. Plates were incubated for 3 hours at 30°C. After incubation the assay buffer was removed by aspiration and the wells were washed 3 times with 200 microliter cold 10 millimolar sodium pyrophosphate in phosphate buffered saline. The last wash was aspirated and blotted plate dry. Plate was then counted on a Packard TopCount.

15 Fluorescence Anisotropy Kinase Binding Assay

The kinase enzyme, fluorescent ligand and a variable concentration of test compound are incubated together to reach thermodynamic equilibrium under conditions such that in the absence of test compound the fluorescent ligand is significantly (>50%) enzyme bound and in the presence of a sufficient concentration (>10x K_i) of a potent inhibitor the anisotropy of the unbound fluorescent ligand is measurably different from the bound value.

The concentration of kinase enzyme should preferably be $\geq 1 \times K_f$. The concentration of fluorescent ligand required will depend on the instrumentation used, and the fluorescent and physicochemical properties. The concentration used must be lower than the concentration of kinase enzyme, and preferably less than half the kinase enzyme concentration. A typical protocol is:

All components dissolved in Buffer of final composition 50 mM HEPES, pH 7.5, 1 mM CHAPS, 1 mM DTT, 10 mM $MgCl_2$ 2.5% DMSO.

ALK5 Enzyme concentration: 4 nM

Fluorescent ligand concentration: 1 nM

30 Test compound concentration: 0.1 nM - 100 uM

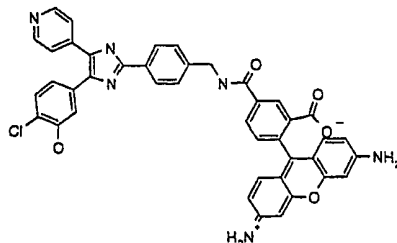
Components incubated in 10 ul final volume in LJJL HE 384 type B black microtitre plate until equilibrium reached (5-30 mins)

Fluorescence anisotropy read in LJJL Acquest.

Definitions: K_i = dissociation constant for inhibitor binding

35 K_f = dissociation constant for fluorescent ligand binding

The fluorescent ligand is the following compound:



which is derived from 5-[2-(4-aminomethylphenyl)-5-pyridin-4-yl-1H-imidazol-4-yl]-2-chlorophenol and rhodamine green.

Inhibition of Matrix Markers: Northern Blot Protocol

- 5 Data confirming activity in the enzyme assay was obtained as follows:
- A498 renal epithelial carcinoma cell lines were obtained from ATCC and grown in EMEM medium supplemented with 10% fetal calf serum, penicillin (5 units/ml) and streptomycin (5ng/ml). A498 cells were grown to near confluence in 100mm dishes, serum-starved for 24 hours, pre-treated with compounds for 4 hours followed by a 10ng/ml addition of
- 10 TGF-beta1 (R&D Systems, Inc., Minneapolis MN). Cells were exposed to TGF-beta1 for 24 hours. Cellular RNA was extracted by acid phenol/chloroform extraction (Chomczynski and Sacchi, 1987). Ten micrograms of total RNA were resolved by agarose gel electrophoresis and transferred to nylon membrane (GeneScreen, NEN Life Sciences, Boston MA). Membranes were probed with 32P-labeled cDNA probes (Stratagene, La Jolla, CA) for fibronectin mRNA.
- 15 Membranes were exposed to phosphorimaging plates and bands were visualized and quantified with ImageQuant software (Molecular Dynamics, Sunnyvale, CA).

Inhibition of Matrix Markers: Western Blot Protocol

- Cells were grown to near confluence in flasks, starved overnight and treated with TGF-beta and compounds. Cells were washed at 24 or 48 hours after treatment with ice cold
- 20 phosphate buffered saline, then 500 microliter of 2X loading buffer was added to plate and cells were scraped and collected in microcentrifuge tube. (2X loading buffer: 100 mM Tris-Cl, pH6.8, 4% sodium dodecyl sulfate, 0.2% bromophenol blue, 20% glycerol, 5% beta-mercapto-ethanol). Cells were lysed in tube and vortexed. Sample was boiled for 10 minutes. 20 microliters of
- 25 sample was loaded on 7.5% polyacrylamide gel (BioRad) and electrophoresed.
- Size fractionated proteins in gel were transferred to nitrocellulose membrane by semidry blotting. Membrane was blocked overnight with 5% powdered milk in phosphate buffer saline (PBS) and 0.05% Tween-20 at 4 degrees C. After 3 washes with PBS/Tween membranes were incubated with primary antibody for 4 hours at room temperature. After three washes with
- 30 PBS/Tween membrane was incubated with secondary antibody for 1 hour at room temperature. Finally, a signal was visualized with ECL detection kit from Amersham.

The compounds generally show ALK5 receptor modulator activity having IC₅₀ values in the range of 0.0001 to 10 μ M.

Claims:

1. A method of treatment of a disease mediated by the ALK5 receptor in mammals, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of an imidazolyl-cyclic acetal as disclosed in WO 98/56788.
2. A method for treating a disease selected from chronic renal disease, acute renal disease, wound healing, arthritis, osteoporosis, kidney disease, congestive heart failure, ulcers, ocular disorders, corneal wounds, diabetic nephropathy, impaired neurological function, Alzheimer's disease, atherosclerosis, peritoneal and sub-dermal adhesion, any disease wherein fibrosis is a major component including lung fibrosis and liver fibrosis, and restenosis, comprising administering to a mammal in need of such treatment, a therapeutically effective amount of an imidazolyl-cyclic acetal as disclosed in WO 98/56788.
3. A method for inhibiting matrix formation in mammals, comprising administering to a mammal, a therapeutically effective amount of an imidazolyl-cyclic acetal as disclosed in WO 98/56788.
4. The use of an imidazolyl-cyclic acetal as disclosed in WO 98/56788 in therapy.
5. The use of an imidazolyl-cyclic acetal as disclosed in WO 98/56788, in the manufacture of a medicament for the treatment of a disease mediated by the ALK5 receptor in mammals.
6. The method or use according to any one of the preceding claims wherein:
 - i) the 5-position of the imidazolyl is substituted by 6-methylpyridin-2-yl; and/or
 - ii) the 4-position of the imidazolyl is substituted by phenyl optionally substituted by halo, or phenyl fused with a 5- to 7-membered aromatic or non-aromatic ring wherein said ring contains up to three heteroatoms, independently selected from N, O and S; and/or
 - iii) the imidazolyl ring nitrogens are unsubstituted or optionally substituted by C₁₋₆ alkyl.
7. The method or use according to claim 6 wherein the 4-position of the imidazolyl is selected from benzo[1,3]dioxolyl, 2,3-dihydrobenzo[1,4]dioxinyl, benzoxazolyl, benzothiazolyl, benzo[1,2,5]oxadiazolyl, benzo[1,2,5]thiadiazolyl, dihydrobenzofuranyl, quinoxalinyl, benzimidazolyl, C₁₋₆ alkylbenzimidazolyl or [1,2,4]triazolo[1,5-a]pyridyl.
8. A compound of WO 98/56788 according to any one of claims 6 or 7 in which the 5-position of the imidazolyl is substituted by 6-methylpyridin-2-yl.
9. A pharmaceutical composition comprising a compound according to any one of claims 6 to 8, or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier or diluent.

INTERNATIONAL SEARCH REPORT

Intel Application No
PC 1, cr 02/00112

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61K31/4178 A61K31/44 A61K31/4427 A61K31/4439 A61K31/444
 A61K31/496 A61K31/505 A61K31/506 A61K31/5377 A61K31/541
 A61P13/12 A61P19/02 A61P19/10 A61P9/10 A61P1/04

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61K A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, BIOSIS, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 98 56788 A (BAMBOROUGH PAUL LINDSAY ; RHONE POULENC RORER LTD (GB); WALLACE PAU) 17 December 1998 (1998-12-17) cited in the application * Tables 1-5; p.45, 1.8-p.46, 1.2; claims 1-43 *	5-9
Y	WO 00 61576 A (BURGESS JOELLE LORRAINE ; SMITHKLINE BEECHAM CORP (US); CALLAHAN JA) 19 October 2000 (2000-10-19) claims 1-12	5-9
Y	WO 99 03837 A (ORTO MCNEIL PHARMACEUTICAL INC) 28 January 1999 (1999-01-28) * p.7, 1.1-8; claims 1-19 *	5-9
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☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
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- *O* document referring to an oral disclosure, use, exhibition or other means
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- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
- *G* document member of the same patent family

Date of the actual completion of the international search

16 May 2002

Date of mailing of the international search report

27/05/2002

Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

Int. Application No.

PCT/EP 02/00112

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61P27/02 A61P3/10 A61P25/28 A61P11/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P, A	WO 01/89556 A (ASHCROFT GILLIAN S ;DENG CHUXIA (US); ROBERTS ANITA B (US); RUSSO) 29 November 2001 (2001-11-29) claims 1-10 -----	5-9

☐ Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

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- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *G* document member of the same patent family

Date of the actual completion of the international search

16 May 2002

Date of mailing of the international search report

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 5-7(part),8-9

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating chronic or acute renal diseases, kidney diseases or diabetic nephropathy, the imidazolyl cyclic acetal derivatives of claim 8 and pharmaceutical compositions according to claim 6 or 7.

2. Claims: 5-7(part)

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating wound healing

3. Claims: 5-7(part)

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating arthritis

4. Claims: 5-7(part)

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating osteoporosis

5. Claims: 5-7(part)

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating congestive heart failure or atherosclerosis or restenosis

6. Claims: 5-7(part)

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating ulcers

7. Claims: 5-7(part)

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating ocular disorders, corneal wounds

8. Claims: 5-7(part)

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating impaired

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

neuological functions, alzheimer's disease

9. Claims: 5-7(part)

Use of imidazolyl cyclic acetal derivatives of W09856788 in the manufacture of a medicament for treating peritoneal and subdermal adhesion, any disease wherein fibrosis is a major component including lung or liver fibrosis

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claim 5 relate to the use of a compound in the manufacture of a medicament for treating a disease defined by reference to a desirable characteristic or property, namely a disease mediated by the ALK5 receptor

The claims cover all of the diseases having this characteristic or property, whereas the application provides support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT for only a very limited number of such a disease. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Independent of the above reasoning, the claims also lack clarity (Article 6 PCT). An attempt is made to define the disease by reference to a result to be achieved. Again, this lack of clarity in the present case is such as to render a meaningful search over the whole of the claimed scope impossible. Consequently, the search has been carried out for those parts of the claims which appear to be clear, supported and disclosed, namely those parts relating to the disease defined in claim 2.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 02/00112

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
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			AU 7925998 A	30-12-1998
			BR 9810007 A	15-08-2000
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